associated Tac-positive cells without affecting normal cells, wherein the therapeutic amount is provided in a ratio of anti-Tac to ^{90}Y conjugate, said ratio comprising [comprises] 2-100 mg of anti-Tac to [wherein] 5-15 mg mCi ^{90}Y conjugate [is provided], said ratio is determined based upon soluble IL-2 receptor levels, such that 25 to 75% saturation of total IL-2 receptors is provided.

24. (amended) A pharmaceutical composition comprising a cytotoxin-conjugated anti-Tac antibody wherein the cytotoxin is selected from the group consisting of ^{90}Y and ricin A and a suitable excipient, provided in an effective dose, wherein the effective dose is provided in a ratio of anti-Tac to cytotoxin-conjugate, said ratio sufficient to produce 25 to 75% saturation of IL-2 receptors by said cytotoxin conjugate.

REMARKS

Applicant respectfully requests favorable reconsideration in view of the herewith presented amendment and remarks.

Claims 1-25 are pending in the instant patent application. Applicant submits that no new matter is added by the present amendment

Support for the recitation of a ratio being determined based upon soluble IL-2 receptor levels is found, *inter alia*, on p. 14, lines 3-10. Support for specific levels of IL-2R saturation is set forth, *inter alia*, on page 15, lines 6-10.

The present invention is directed to a method for treating disease associated with elevated levels of Tac-positive cells in humans using anti-Tac conjugates and

administrating the anti-Tac conjugates in a specific ratio so that 25-75% of the IL-2 receptors are saturated. The necessity for the proper ratio as well as the means for determining the proper ratio is provided in the instant specification. The present invention arises from the difficulties in the art in providing a balance between antibody and cytotoxic agent. When small quantities of ^{90}Y conjugated anti-Tac are administered to patients with high levels of soluble IL-2 receptors (IL-2R) the ^{90}Y conjugated anti-Tac forms a complex with the circulating IL-2R and, therefore, is unable to bind to the tumor cells efficiently. On the other hand, if the total amount of anti-Tac administered is too large, the tumor cell surface receptors become saturated and much of the radio-labelled antibody remains in the plasma and unbound to the tumor cells, thereby reducing the proportion of cytotoxic agent being delivered to the target cells while increasing the concentration of cytotoxic agent delivered to normal cells. The present invention has identified that optimal dosing is produced by saturating 25-75% of the IL-2 receptors. In addition, the present invention has revealed that this dosage range is determined by the patient's IL-2R level. It is this aspect of the present invention which clearly provides a therapeutic advantage in treating disease.

Claims 1-14, 16, 17, 19-25 have been rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Waldmann (Ann. Oncol., 1994; 1449). Applicant respectfully disagrees with these rejections.

The Waldmann article, in general, describes four methods potentially useful in anti-Tac treatment of disease. The first method uses murine antibodies, the second humanized antibodies, the third antibody-toxin conjugates and the fourth method uses antibody-radionuclide conjugates.

As to the first method, the Waldmann article states that murine antibodies are unsuitable for treatment of lymphomas because their effectiveness is limited by the neutralizing effect of host immune response (p. 15, col. 1). In addition, Waldmann indicates that the murine antibodies are relatively ineffective as cytocidal agents (p. 15, col. 1). Applicant notes that other Waldmann articles (i.e. Science 1991, 252, 1657-1662, attached as Exhibit 1) also indicate murine antibodies are ineffective treatment and "disappointing" (p. 1657, col. 2). A person skilled in the art would have been discouraged from pursuing a method of anti-Tac treatment using murine antibodies at the time of the instant invention.

The second method of treatment discussed in Waldmann (Ann. Oncol.) uses unlabelled humanized IL-2R antibodies. The article describes humanized anti-Tac antibodies and their immunogenic testing in cynomolgus monkeys.

The third method described in Waldmann (Ann. Oncol.) deals with anti-Tac antibodies conjugated to immunotoxins. These conjugates were found to produce "limited activity" in humans according to Waldmann (p. 15). The cited Waldmann article provides no teaching or suggestion as to conjugate in proper ratio of immunotoxin.

The Waldmann reference also proposes a method of treating human patients with anti-Tac antibodies which are chelated to radionuclides. Alpha-emitting radionuclides and β-emitting radionuclides were considered. A related Waldmann review article in *Science* (1991, attached hereto as Exhibit 1) addresses the preference of α-emitting radionuclides over β-emitting radionuclides stating: "[t]hus, one of the most promising directions for future development of armed monoclonal antibodies for the treatment of cancer involves the chelation of α-emitting radionuclides to human or humanized monoclonal antibodies".

Therefore at the time of the present invention, one skilled in the art would have preferred α-emitting radionuclide and avoided β-radionuclides.

The instant invention claims a method of treating disease in humans using ^{90}Y-conjugated anti-Tac antibody provided in a specific ratio. Waldmann (Ann. Oncol.) provides no teaching or suggestion regarding the claimed effective dosage; i.e. the ratio of conjugated anti-Tac to non-conjugated anti-Tac. Applicant submits that since the Waldmann article fails to teach every element of the claims, the reference is not anticipatory under 35 U.S.C. §102. Further, the Waldmann article does not render the claimed invention obvious under 35 U.S.C. §103 because (1) the reference fails to teach or suggest a specific ratio of conjugated antibody and (2) the reference fails to teach or suggest the degree of saturation required to provide an effective dosage. For these reasons, the consideration and withdrawal of the rejection is respectfully requested.

Claims 1-14, 16, 17, 19-25 have been rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Waldmann (Imp. Adv. Oncol., 1994). Applicant respectfully disagrees with these rejections.

This Waldmann article (Imp. Adv. Oncol.), in general, describes the same four methods for anti-Tac treatment as discussed in Waldmann (Ann. Oncol.). The first method deals with murine antibodies, the second with humanized antibodies, the third with antibody-toxin conjugates and the fourth method with antibody-radionuclide conjugates.

Just as Waldmann (Ann. Oncol.), Waldmann (Imp. Adv. Oncol.) states that murine antibodies are unsuitable for treatment of lymphomas due to their limited

effectiveness because of short survival time in humans. A person skilled in the art would have been dissuaded from using such a method of treatment at the time of the invention. As to the use of unlabeled humanized IL-2R antibodies, Waldmann describes the numerous problems associated with developing chimeric proteins such as, significant loss of binding and substantially altered pharmacokinetics observed in monkeys. As to the use of anti-Tac antibodies immunotoxins conjugated, Waldmann states that many of these conjugates showed "limited activity" against human T cells while others produced "unacceptable liver damage" in cynomolgus monkeys. Lastly, Waldmann proposed a method for use of anti-Tac antibodies which are chelated to radionuclides. The two groups of radionuclides considered are α-emitting radionuclides and β-emitting radionuclides.

The instant invention is directed to a method of treating (1) disease in (2) humans using (3) ^{90}Y-conjugated anti-Tac antibody provided in a (4) specific ratio of anti-Tac to ^{90}Y. There is no teaching or suggestion in Waldmann (Imp. Adv. Oncol.) regarding the effective dosage; i.e. the ratio of conjugated anti-Tac to non-conjugated anti-Tac. As set forth in the instant specification (p. 17), the ratio of anti-Tac to ^{90}Y-conjugate greatly facilitates the effectiveness of the instant method and thus is an important attribute of the claimed invention. Reconsideration and withdrawal of this rejection is respectfully requested.

Claims 1-14, 16, 17, 19-25 have been rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Waldmann (Leukemia, 1993) 1994). Applicant respectfully disagrees with these rejections.

This Waldmann (Leuk.) reference proposes the same methods of treating disease as described in Waldmann (Ann. Oncol.) and Waldmann (Imp. Adv. Oncol.). As

discussed above, none of the methods described in these articles teaches or suggests a specific ratio of anti-Tac to ^{90}Y conjugate capable of producing 25%-75% saturation of IL-2R. The ratio of anti-Tac and ^{90}Y conjugate recited in the instant claims is critical to the effectiveness of the present invention. Waldmann (Leuk.) neither teaches or suggests the claimed ratios. Hence, applicant urges that the instant claims are neither anticipated nor obvious in view of Waldmann (Leuk.). Reconsideration and withdrawal of this rejection is respectfully requested.

Claims 1-14 and 16-25 are rejected under 35 U.S.C. § 103 as being unpatentable over Waldmann (Ann. Oncol., 1994; 1449) or Waldmann et al. (Imp. Adv. Oncol., 1994) or Waldmann (Leukemia, 1993) in view of Hakimi (J. Immunol., 1991), Waldmann et al. (Blood, 1993) and Kreitman et al. (Bioconjugate Chem., 1993). Applicant respectfully disagrees with these rejections.

As discussed above, the three Waldmann review articles fail to provide the skilled artisan with sufficient guidance as to the specific ratio of anti-Tac to ^{90}Y conjugate necessary to provide an effective dose. Hence, these articles do not render the present invention obvious.

The Waldmann (Blood) paper describes treating disease in humans using ^{90}Y conjugated anti-Tac. It does not, however, teach the therapeutically effective amount to be administered to a patient; i.e. the ratio of conjugated to unconjugated anti-Tac claimed in the instant invention.

Hakimi et al. describes humanized antibodies being administered to monkeys in order to determine the pharmacokinetics of humanized antibodies as compared to murine

antibodies. The Hakimi et al. article does not provide any teaching or suggestion of a specific antibody-radionuclide ratio which is missing from the Waldmann articles and claimed in the present invention. Thus, Hakimi adds nothing to the cited Waldmann article as it relates to the patentability of the present invention.

Kreitman et al. describes modified toxins conjugated to anti-Tac *in vitro* assays and related pharmacokinetics studies in mice. Kreitman does not teach or suggest the treatment of disease in humans using a conjugated anti-Tac in the specific ratio presently claimed.

If the skilled artisan were to combine the teachings of the Waldmann articles, Hakimi and Kreitman, the artisan would not recognize the present invention as claimed. None of the cited references either alone or in combination teach or suggest the specific ratio necessary to provide an effective dose capable of achieving specific levels of IL-2 receptor saturation. None of these references alone or in combination provide the skilled artisan with sufficient guidance to identify the correct therapeutic amount as set forth in the instant claims. Therefore, applicant respectfully requests reconsideration and withdrawal of the pending rejection.

Claim 15 is rejected under 35 U.S.C. § 103 as being unpatentable over Waldmann (Ann. Oncol., 1994; 1449) or Waldmann et al. (Important Adv. Oncol., 1994) or Waldmann (Leukemia, 1993) in view of Hakimi (J. Immunol., 1991), Waldmann et al. (Blood, 1993) and Kreitman et al. (Bioconjugate Chem., 1993) as applied to claims 1-14 and 16-25 above and in further view of Parenteau et al. (Transplantation). Applicant respectfully disagrees with this rejection.

The Waldmann articles, the Hakimi article, and the Kreitman article (discussed above), taken together or separately, do not teach or suggest the therapeutically effective dosages claimed. The Examiner asserts that Parenteau teaches the use of G-CSF in combination with ^{90}Y-conjugated anti-Tac treatment. Applicant respectfully disagrees with this assessment of Parenteau.

The instant invention claims a method of treating disease in humans using ^{90}Y-conjugated antibody in a specific ratio and further providing G-CSF. While the Parenteau reference describes the use of G-CSF, it does not teach or suggest the proper therapeutic amount for treatment of humans necessary to provide effective levels of receptor saturation. In fact, the very high dosages of conjugates given to the monkeys in the Parenteau reference, and the fact that 60% of the monkeys receiving ^{90}Y-conjugated anti-Tac therapy died adds to the uncertainty of determining the proper therapeutic amount to be administered to humans. Therefore, Parenteau when viewed in combination with the other references relied upon by the Examiner, does not provide the skilled artisan guidance in determining the specific ratio of anti-Tac to ^{90}Y conjugate necessary for providing an effective dosage. Reconsideration and withdrawal of this rejection is respectfully requested.

Claims 24-25 are rejected under 35 U.S.C. § 103 as being unpatentable over Kozak et al. (PNAS, 1986) or Diamantstein et al. (Immunol. Rev., 1986) in view of Order et al. (Int. J. Radiat. Ocol. Biol. Phys., 1986) or Wessels et al. (Med. Phys., 1984). The applicant respectfully disagrees with this rejection.

Kozak et al. describes the use of ^{212}Bi-conjugated anti-Tac for the treatment of adult T-cell leukemia. Kozak provides no disclosure of any *in vivo* use of ^{90}Y-conjugated

anti-Tac. In fact, the Kozak article leads away from the instant invention in that it would discourage the skilled artisan from using β-emitting radionuclides for therapy.

The Diamantstein article describes attempts to find an IL-2 receptor for immunosuppressive therapy. Diamantstein is merely a review article discussing the interleukin-2 receptor and approaches to selective immunosuppressive therapy by anti-IL-2 receptor monoclonal antibodies. However, the review article is completely silent on the use of radionuclides in immunosuppressive therapy. Therefore, applicant submits that the Diamantstein article is irrelevant in evaluating the patentability of the instant application.

Order et al. describes the possible use of ^{90}Y conjugated to anti-ferritin antibodies for the treatment of cancer. External radiation of the primary tumor in advance of the use of ^{90}Y-antiferritin, described by Order, provided increased antibody uptake and increased tumor dose rate and total dose. The treatment described in the Order reference is given in conjunction with an external source of radiation. The Order article does not supplement the cited art in any way as to teach or suggest the missing teaching of specific anti-Tac to ^{90}Y conjugate ratios to provide an effective dose.

The Wessels article describes theoretical calculations used to describe possible dosages of a variety of radionuclides including ^{90}Y. This articles discusses the possibility of ^{90}Y to be used as a therapeutic agent in combination with antibodies. However, the article does not specify which radionuclides would be preferred agents. Further, Wessels does not teach or suggest the critical ratio of anti-Tac to ^{90}Y conjugate needed to provide an effective dosage.

Applicant submits that none of Kozak, Diamantstein, Order or Wessels, taken alone or in combination teach or suggest the specific ratios of anti-Tac to ^{90}Y conjugate necessary for an effective dose, as presently claimed. In fact, Kozak specifically indicates a preference for α-emitting radionuclides. Neither Order nor Wessels relate to radioimmunosuppression and therefore add nothing to the cited art as it relates to the claimed invention. For these reasons, applicant respectfully requests reconsideration and withdrawal of the §103 rejection.

Allowance of the pending claims is respectfully requested. Early and favorable action by the Examiner is earnestly solicited.

AUTHORIZATION

No additional fee is believed to be necessary.

The Commissioner is hereby authorized to charge any additional fees which may be required for this amendment, or credit any overpayment to Deposit Account No. 13-4500, Order No. 2026-4003US3.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition and for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or

credit any overpayment for an extension of time to Deposit Account No. 13-4500, Order No. 2026-4003US3.

A DUPLICATE COPY OF THIS SHEET IS ATTACHED.

Respectfully submitted,
MORGAN & FINNEGAN, L.L.P.

Dated: June 4, 1997

By: Dorothy R. Auth
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